A Comparison of Methods Used to Evaluate Intakes of Transuranics Influenced by Chelation Therapy

by

T. La Bone

Westinghouse Savannah River Company
Savannah River Site
Aiken, South Carolina 29808

A document prepared for HPS SUMMER SCHOOL ON INTERNAL DOSIMETRY at Gainesville, FL, USA from 6/10/2002 - 6/14/2002.

DOE Contract No. **DE-AC09-96SR18500**

A Comparison of Methods Used to Evaluate Intakes of Transuranics Influenced by Chelation Therapy

Health Physics Summer School on
Practical Applications of Internal Dosimetry
University of Florida
Gainesville, Florida
June 10-14, 2002

Thomas R. La Bone
Westinghouse Savannah River Company

Introduction

At the 1994 HPS Summer School on Internal Dosimetry[a], I presented a review of the Hall method for evaluating urinary excretion data influenced by chelation therapy (La Bone 1994). Since that time several events have occurred:

- Hall's method has been applied to dozens of plutonium intake cases, primarily historic ones, involving chelation therapy.
- Some internal dosimetrists have expressed some reservations about the method.
- Work on a recent plutonium intake case at LANL promoted the development of a new method for evaluating urinary excretion data influenced by chelation therapy. This new method is less empirical and more mechanistic than the Hall method, and as a result is referred to as the "mechanistic method."
- All methods have been coded in Mathcad[b].

The purpose of this paper is to introduce the mechanistic method by using it to validate Hall's method and Jech's method[c]. This is accomplished by using the mechanistic method to generate a known set of data suitable for benchmarking all three methods. Three appendices are provided to document the benchmarking:

- Appendix A is a Mathcad worksheet that details for all three methods the evaluation of urine bioassay data following an inhalation intake of Type M plutonium.
- Appendix B is a concise review of Hall's method.
- Appendix C is a Mathcad worksheet that details how the benchmark data were generated for an inhalation intake of Type M plutonium.

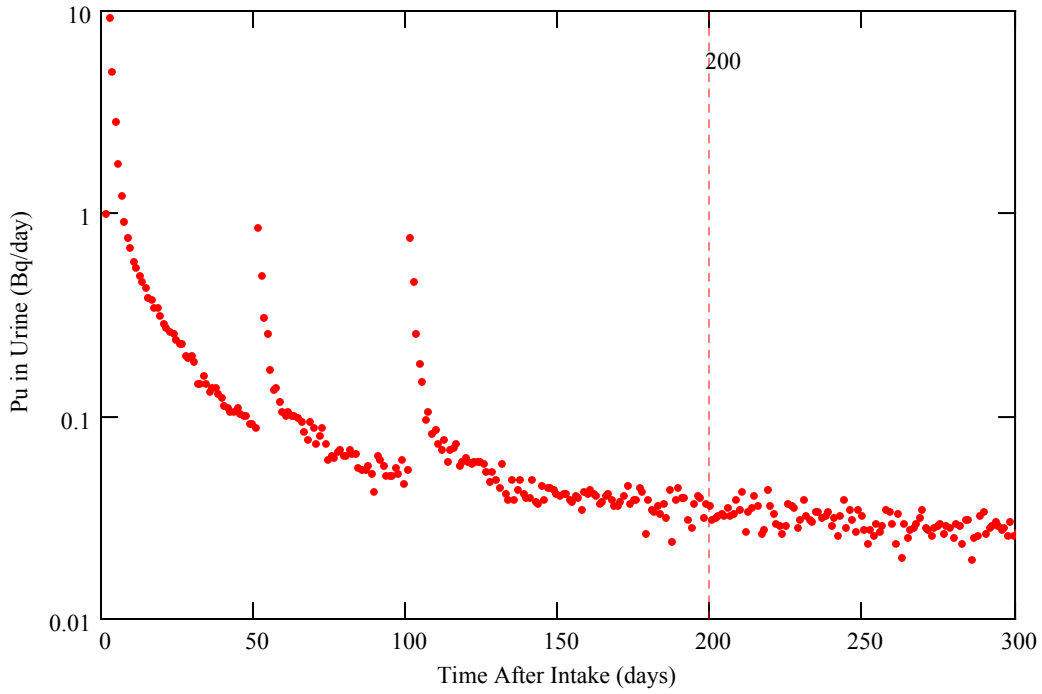
Inhalation intakes of Type S plutonium and injection intakes will also be discussed, but detailed worksheets are not provided for these materials.

[a] *Internal Radiation Dosimetry*, O. G. Raabe, editor. (Madison: Medical Physics Publishing) 1994.
[b] Mathsoft Education and Engineering Inc., Cambridge, MA.
[c] Jech, JJ. et al., *Interpretation of Human Urinary Excretion of Plutonium for Cases Treated with DTPA* Health Physics (22) pp. 787-792, 1972.

Jech's Method

The observed[d] urinary excretion $e_{obs}(t)$ of plutonium-239 following an acute inhalation intake of 1.0 μm AMAD Type M aerosol is shown in Figure 1.

Figure 1. Urinary excretion following and inhalation intake of 1.0 μm AMAD Type M plutonium-239 aerosol.



This individual was chelated three times, once each day at 1, 50, and 100 days after intake. Remember that chelations are specified at the beginning of the day and incremental urinary excretion at the end of the day, so the chelation at t=1 day after intake influences the urinary excretion on day 2 and not day 1.

The chelation therapy elevates the urinary excretion rate of plutonium-239 for approximately 100 days after the last chelation. Thus, we will use Jech's method only on the urinary excretion after day 200. Given that $i_u(t)$ is the function that generates urinary excretion fractions, the array of intake retention fractions ε for times t_{200} through t_{300} is given by

$$\varepsilon_i = i_u(t_i) \qquad (1)$$

Note that the values of the **ε** array do not account for the effects of chelation in any way. The unweighted least squares estimate of the intake is given by

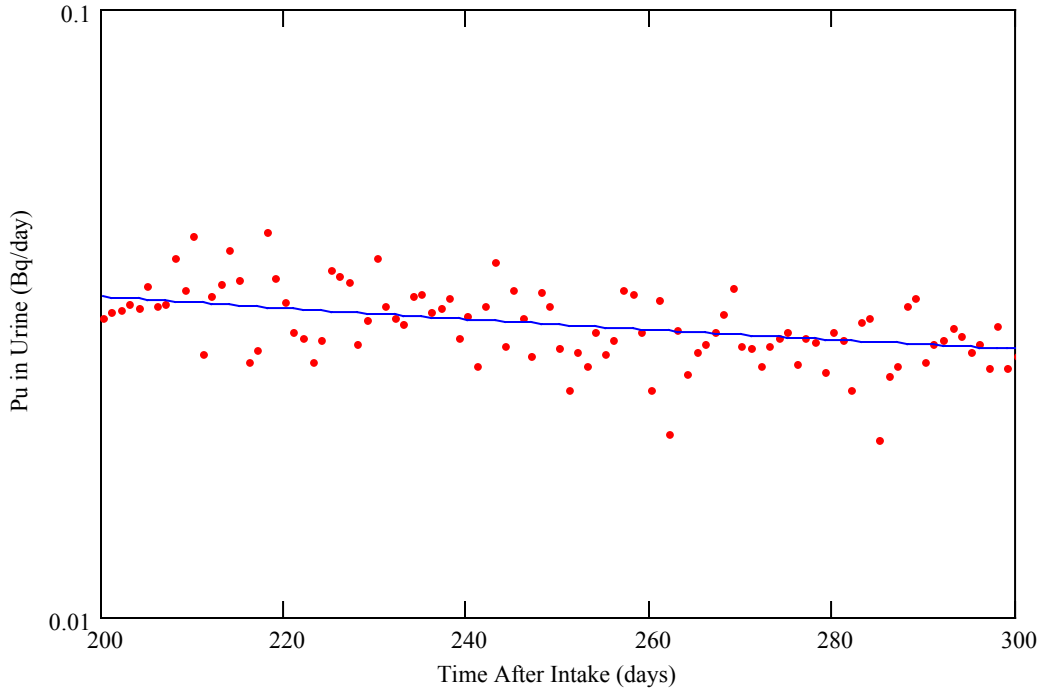
$$I_{eff} = \left[\left(\varepsilon^T \varepsilon\right)^{-1}\left(\varepsilon^T e_{obs}\right)\right] \qquad (2)$$

In this equation the T superscript indicates the transpose of the matrix and the –1 superscript the inverse of the matrix. The intake calculated by this method will be referred to as the *effective intake* and will be denoted by I_{eff}. The effective intake[e] for this case is 4298 Bq. The details of this calculation are shown in Appendix A. The product of I_{eff} and ε_i gives the predicted or

[d] The method used to generate this "synthetic data" is discussed in Appendix C.
[e] Rounded to the nearest whole Bq.

expectation urinary excretion e_{exp} at the i^{th} day after intake. The plot of the observed versus the predicted excretion is shown in Figure 2.

Figure 2. Plot of observed and predicted urinary excretion from Jech's method.



The effective intake is used to calculate the dose. The intake to dose conversion factor for 1.0 μm AMAD Type M plutonium-239 is

$$DCF_m = 3.31\times10^{-5}\,\frac{Sv}{Bq}$$

The committed effective dose H_e calculated from the effective intake is the product of I_{eff} and DCF_m, to three significant digits is

$$H_e = (4298\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right) = 0.142\,Sv \qquad (3)$$

Jech's method is simple to use but has the following disadvantages:

- We must wait for the effects of chelation to subside before an effective intake can be calculated.
- No estimate of the effectiveness of chelation therapy is provided by the method.

Hall's method was developed to address both of these disadvantages, giving an estimate of I_{eff} in a more timely fashion while at the same time giving an estimate of the effectiveness of the chelation therapy.

Hall's Method

Hall's method was reviewed at the 1994 HPS Summer School on Internal Dosimetry. An updated summary of the method is given in Appendix B of this report. In Hall's method, an intake of plutonium treated with a chelation agent is evaluated in the following way:

- Specify the biokinetic model for the intake.
- Generate the intake retention fractions for the intake at the P times when excretion data are available.
- Specify i_c and E for the chelation model.
- Generate the apparent intake retention fractions for the intake and N chelations at the P times when excretion data are available.
- Calculate the least squares estimate I of the intake.
- Multiply the intake I by the apparent intake retention fractions and sum to produce the expectation urinary excretion $e_{obs}(t)$.
- Calculate the effective intake I_{eff} and use it to calculate the committed equivalent dose.

The urinary excretion data was evaluated with Hall's method assuming an enhancement factor E of 18.5 along with the following chelate excretion function (see Appendix B):

$$i_c(t-\tau) = 0.6073\left[0.95e^{\frac{-\ln(2)(t-\tau)}{1}} + 0.05e^{\frac{-\ln(2)(t-\tau)}{10}}\right] \qquad (4)$$

The intake I, quantity q of plutonium removed by chelation, and effective intake I_{eff} calculated with Hall's method using an unweighted least squares fit are

$$I = 4312\,Bq$$
$$q = 33\,Bq$$
$$I_{eff} = 4312\,Bq - 33\,Bq = 4279\,Bq \qquad (5)$$

The plot of the predicted and observed urinary excretion is shown in Figure 3. Using the effective intake, the dose is

$$H_e = (4279\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right) = 0.142\,Sv \qquad (6)$$

Alternatively, the dose can be calculated assuming that q gives the same dose as an injection intake. Thus, the dose is

$$H_e = I\,DCF_m - q\,DCF_{inj} \qquad (7)$$

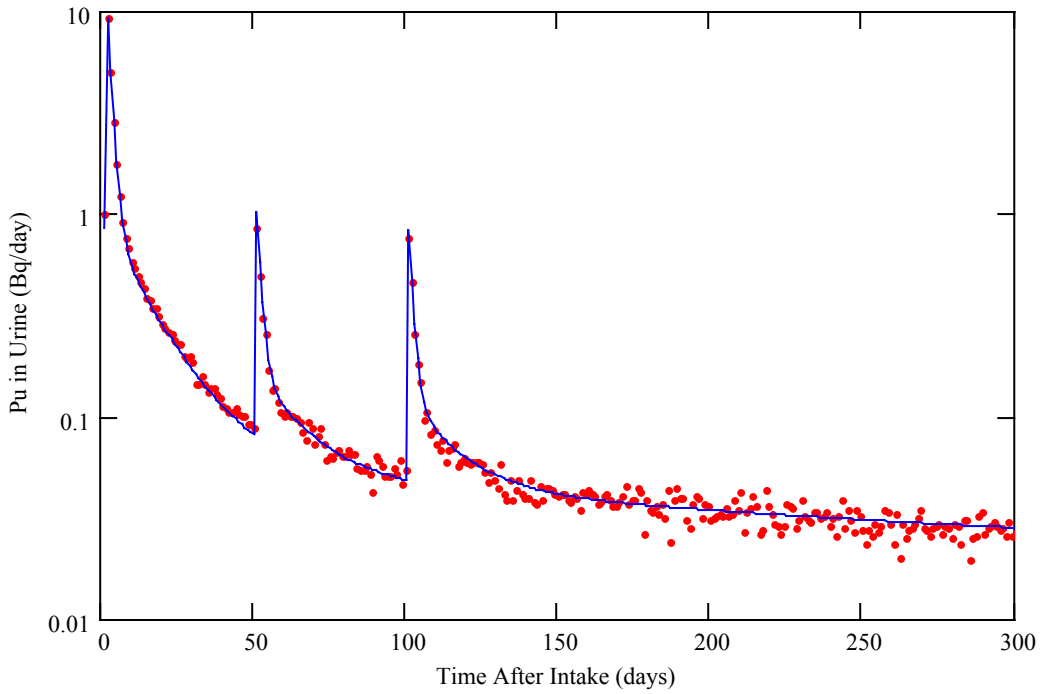
Note that I and not I_{eff} is used in Equation 7. DCF_{inj} is the intake to dose conversion factor for an instantaneous quantitative uptake of plutonium-239:

$$DCF_{inj} = 5.03\times10^{-4}\,\frac{Sv}{Bq}$$

Using this approach, the dose is

$$H_e = (4312\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right) - (33\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right) = 0.126\,Sv \qquad (8)$$

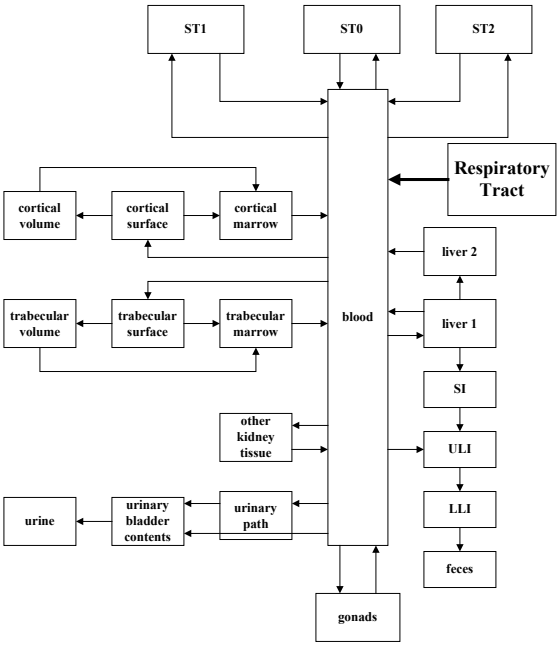
Figure 3. Plot of observed and predicted urinary excretion from Hall's method.



Mechanistic Method

The Hall chelation model works on the simple premise that the plutonium available for chelation is proportional to the amount of plutonium in the urine. A more direct approach would be to model the effects of chelation in the compartments of the body where the chelation agent actually works. At the time the Hall model was developed this approach was not practical, primarily because the most accurate urinary excretion models available were empirical models. These empirical models, like the Jones urinary excretion function, describe urinary excretion as a function of time but do not provide any information on biokinetics of plutonium in the body.

In the mid 1990's, mechanistic models such as the ICRP 67 systemic model for plutonium and the ICRP 66 respiratory tract model became available. The ICRP 66/67 model for plutonium looks something like this:



The single compartment labeled "respiratory tract" is actually a complex system of compartments that are used to model

- the deposition of aerosols in the respiratory tract,
- mechanical clearance of particles from the respiratory tract, and
- dissolution of particles and subsequent absorption of material into the bloodstream.

The structure of the ICRP 66/67 model suggests a simple and direct approach to modeling chelation therapy:

- Start the model with an inhalation intake at t=0 days.
- At the time of chelation, stop the model and remove some plutonium from the compartments where the DTPA-Pu chelate is assumed to form.
- Take this chelate and let it be excreted with its own excretion function (the same function used in Hall's method).
- Restart the model with the new compartment contents as if nothing had happened and calculate the urinary excretion of plutonium.
- Add the excretion of chelate and the excretion of plutonium to get the total excretion.

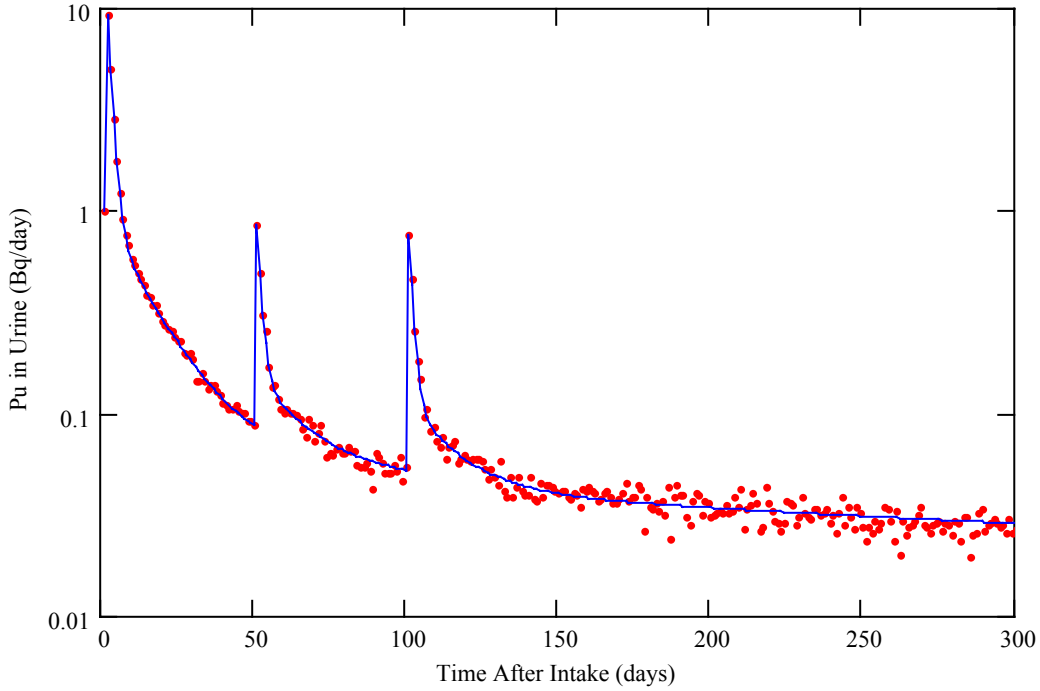
In Hall's method, we specified the chelate excretion function $i_c(t-\tau)$ and the enhancement factor E. The mechanistic method uses the same chelate excretion function but in place of E we need to specify the chelation removal fraction F for each compartment. For example, in this particular case it is assumed that a single dose of DTPA will bind with 0.5 of what is in the blood and 0.023 of what is in the LIV1 compartment. Thus F_{blood}=0.5 and F_{LIV1}=0.023. The details of the calculation are given in a Mathcad worksheet in Appendix A.

The intake I, quantity q of plutonium removed by chelation, and effective intake I_{eff} calculated with the mechanistic method using an unweighted least squares fit are

$$I = 4974\,Bq$$
$$q = 33\,Bq$$
$$I_{eff} = 4974\,Bq - 33\,Bq = 4941\,Bq \qquad (9)$$

The plot of the predicted and observed urinary excretion is shown in Figure 4.

Figure 4. Plot of observed and predicted urinary excretion from the mechanistic method.



Using the effective intake, the dose is

$$H_e = (4941\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right) = 0.164\,Sv \qquad (10)$$

As with Hall's method, the dose can be calculated assuming that q gives the same dose as an injection intake. Using this approach, the dose is

$$H_e = (4974\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right) - (33\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right) = 0.148\,Sv \qquad (11)$$

Discussion of Results

A summary of the results generated by the three different evaluation methods is given in Table 1 for an inhalation intake of a Type M plutonium aerosol. By definition, Jech's method gives the "correct" effective intake. Hall's method (Equation 5) gives essentially the same effective intake as Jech's method, which is not surprising because it was designed to do just that. In comparison, the mechanistic method (Equation 9) tends to overestimate the effective intake. This is because q is a systemic deposition and not an intake, which means that technically

$$I_{eff} \neq I - q$$

The intake (not the effective intake) calculated with the Hall method indirectly reflects that fact that removing q Bq from the systemic compartment reduces the urinary excretion rate considerably more than removing q Bq from the intake. This means that the mechanistic method cannot be used to calculate the effective intake as defined by Jech's method.

The mechanistic method, assuming q gives the same dose as an injection (Equation 11), is considered to give the best estimate of dose to the individual[f]. The doses calculated from the Jech and Hall effective intakes (Equations 3 and 6, respectively), closely approximate the dose from the mechanistic method.

Table 1. Summary of results of Jech, Hall, and mechanistic methods for Type M material.

	I (Bq)	I_{eff} (Bq)	q (Bq)	I_{eff} Dose (Sv)	I&q Dose (Sv)
Jech		4298.0		0.142	
Hall	4312.4	4279.5	32.9	0.142	0.126
Mech	4974.0	4941.4	32.6	0.164	0.148

The fractional dose reduction achieved by the chelation therapy, as calculated with the mechanistic method, is

$$\frac{(33\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right)}{(4974\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right)} = 0.101$$

[f] Treating q as an injection intake is an approximation that nevertheless provides answers adequate for the purpose of this discussion.

Thus, the chelation therapy reduced the dose by about 10%. With Hall's method, the fractional dose reduction is calculated to be

$$\frac{(33\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right)}{(4321\,Bq)\left(3.31\times10^{-5}\,\frac{Sv}{Bq}\right)}=0.116$$

A summary of the results for Type S plutonium are given in Table 2. Chelation therapy removes very little of the intake because the material is not absorbed into the bloodstream to any great extent. For this material, all three methods give essentially the same answers for intake and dose.

Table 2. Summary of results of Jech, Hall, and mechanistic methods for Type S material.

	I (Bq)	I_{eff} (Bq)	q (Bq)	I_{eff} Dose (Sv)	I&q Dose (Sv)
Jech		5073.9		0.0427	
Hall	5120.5	5120.1	0.42	0.0431	0.0429
Mech	5057.0	5056.6	0.42	0.0425	0.0423

The fractional reduction in dose for Type S plutonium, as estimated with the mechanistic method, is

$$\frac{(0.42\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right)}{(5057\,Bq)\left(8.41\times10^{-6}\,\frac{Sv}{Bq}\right)}=0.00497$$

By Hall's method, the reduction is

$$\frac{(0.42\,Bq)\left(5.03\times10^{-4}\,\frac{Sv}{Bq}\right)}{(5120\,Bq)\left(8.41\times10^{-6}\,\frac{Sv}{Bq}\right)}=0.00491$$

A summary of the results for an injection of plutonium are given in Table 3. As expected, chelation therapy is most effective for an injection intake where all of the material is in the systemic compartment.

Table 3. Summary of results of Jech, Hall, and mechanistic methods for an injection.

	I (Bq)	I_{eff} (Bq)	q (Bq)	I_{eff} Dose (Sv)
Jech		3659		1.840
Hall	4845	3667	1178	1.845
Mech	5016	3826	1190	1.925

The fractional reduction in dose (and intake in this case) as calculated with the mechanistic method is

$$\frac{(1190\,Bq)}{(5016\,Bq)} = 0.237$$

which is essentially the same as calculated with Hall's method

$$\frac{(1178\,Bq)}{(4845\,Bq)} = 0.243$$

Conclusions and Recommendations

Based on these observations, the following conclusions and recommendations are made:

- All three methods are capable of giving reasonable estimates of dose after chelation therapy has ceased and no longer influences urinary excretion rates.
- Jech's method should be considered for complex cases that cannot be adequately modeled with the Hall or mechanistic methods.
- Either the Hall or mechanistic method may be used for dose estimates during chelation therapy. The Hall method is computationally less demanding but lacks the technical appeal of the mechanistic method.
- Both the Hall and mechanistic methods are capable of giving comparable estimates of the quantity q of plutonium removed by chelation and both can be used for planning therapy regimens. However, it should be noted that the mechanistic method is considered to give a more accurate estimate of the true intake I.
- The mechanistic method cannot be used to calculated effective intake.

Appendix A

Benchmark for Three Chelation Evaluation Methods

Comparison of three different approaches (the Jech, Hall, and the mechanistic methods) to evaluating urinary excretion following an inhalation intake of Type M plutonium treated with chelation. Implemented in Mathcad 2001i.

Section 1. Define the ICRP 66/67 urinary excretion function

In the first section of this worksheet, we will derive the eigenvalues and coefficients that define the retention functions for all compartments of the ICRP 66/67 biokinetic model.

ORIGIN ≡ 1 Defines arrays to begin with the 1,1 element.

The compartments in the model are assigned numbers to clarify their use in the arrays to be defined.

Respiratory tract compartments. Inhaled particles are deposited in compartments AI1 through ET1.

AI1 := 1	bb1 := 4	BB1 := 7	ET2 := 10	LNet := 13
AI2 := 2	bb2 := 5	BB2 := 8	ETseq := 11	LNth := 14
AI3 := 3	bbseq := 6	BBseq := 9	ET1 := 12	

Transformed respiratory tract compartments.

TAI1 := 15	Tbb1 := 18	TBB1 := 21	TET2 := 24	TLNth := 27
TAI2 := 16	Tbb2 := 19	TBB2 := 22	TETseq := 25	
TAI3 := 17	Tbbseq := 20	TBBseq := 23	TLNet := 26	

GI tract compartments and feces.

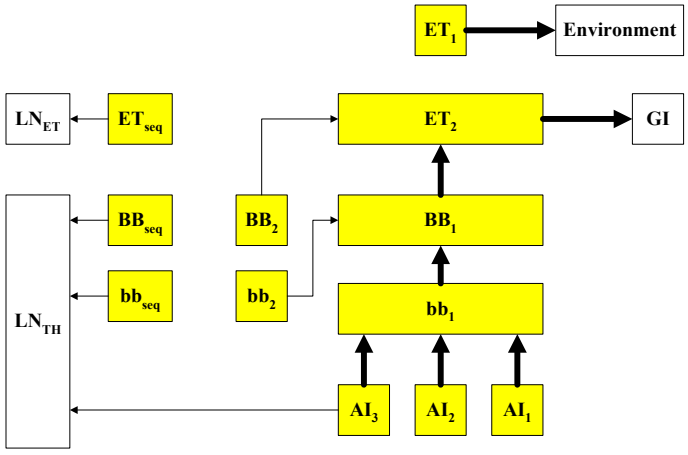
S := 28 SI := 29 ULI := 30 LLI := 31

Systemic compartments of the ICRP 67 plutonium model.

blood := 32	ST0 := 35	CV := 38	TV := 41	OKT := 44	nads := 47	feces := 49
LIV1 := 33	ST1 := 36	CS := 39	TS := 42	UP := 45	ENV := 48	urine := 50
LIV2 := 34	ST2 := 37	CM := 40	TM := 43	UBC := 46		

Define initial deposition in compartments of the respiratory tract.

The mechanical clearance model for the respiratory tract is shown below. Inhaled particles are deposited in the twelve compartments highlighted in yellow. The fractions of particles deposited in compartments AI1 through ET1 following an inhalation intake of 1.0 μm AMAD aerosol are assigned to q0. These values are taken from tables in the ICRP CD.

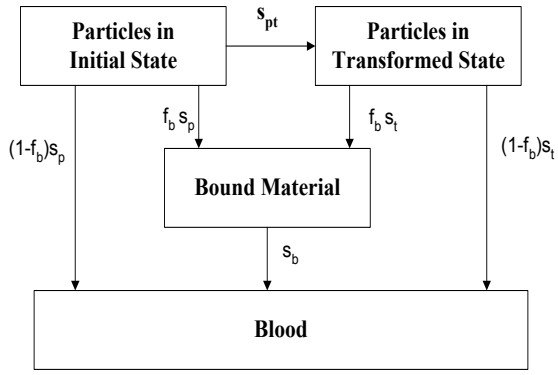


$$q0 := \begin{pmatrix} 0.03198 \\ 0.06396 \\ 0.01066 \\ 0.00833 \\ 0.00809 \\ 0.00012 \\ 0.00649 \\ 0.00584 \\ 8.694 \times 10^{-5} \\ 0.2111 \\ 0.00011 \\ 0.1652 \end{pmatrix}$$

$$q0_{urine} := 0$$

Define particle dissolution model. All rate constants are in units of 1/days.

The dissolution model for the respiratory tract is shown below. Defaults for Type M material are f_r=0.1, s_r=100, s_s=0.005, and f_b=0.



$f_r \equiv 0.1$ $s_r \equiv 100$ $s_s \equiv 0.005$

$s_p := s_s + f_r \cdot (s_r - s_s)$ $s_{pt} := (1 - f_r) \cdot (s_r - s_s)$ $s_t := s_s$

$s_p = 10.00450$ $s_{pt} = 89.99550$ $s_t = 0.00500$

Define transfer rate constants for the respiratory tract compartments.

$k_{AI1,bb1} := 0.02$ $k_{bb2,BB1} := 0.03$ $k_{ETseq,LNet} := 0.001$

$k_{AI1,blood} := s_p$ $k_{bb2,blood} := s_p$ $k_{ETseq,blood} := s_p$

$k_{AI1,TAI1} := s_{pt}$ $k_{bb2,Tbb2} := s_{pt}$ $k_{ETseq,TETseq} := s_{pt}$

$k_{AI2,bb1} := 0.001$ $k_{BB1,ET2} := 10$ $k_{BBseq,LNth} := 0.01$

$k_{AI2,blood} := s_p$ $k_{BB1,blood} := s_p$ $k_{BBseq,blood} := s_p$

$k_{AI2,TAI2} := s_{pt}$ $k_{BB1,TBB1} := s_{pt}$ $k_{BBseq,TBBseq} := s_{pt}$

$k_{AI3,bb1} := 0.0001$ $k_{BB2,ET2} := 0.03$ $k_{bbseq,LNth} := 0.01$

$k_{AI3,LNth} := 0.00002$ $k_{BB2,blood} := s_p$ $k_{bbseq,blood} := s_p$

$k_{AI3,blood} := s_p$ $k_{BB2,TBB2} := s_{pt}$ $k_{bbseq,Tbbseq} := s_{pt}$

$k_{AI3,TAI3} := s_{pt}$ $k_{ET2,S} := 100$ $k_{LNth,TLNth} := s_{pt}$

$k_{bb1,BB1} := 2$ $k_{ET2,blood} := s_p$ $k_{LNet,blood} := s_p$

$k_{bb1,blood} := s_p$ $k_{ET2,TET2} := s_{pt}$ $k_{LNet,TLNet} := s_{pt}$

$k_{bb1,Tbb1} := s_{pt}$ $k_{ET1,ENV} := 1$ $k_{LNth,blood} := s_p$

Define transfer rate constants for the transformed respiratory tract compartments.

$k_{TAI1,Tbb1} := k_{AI1,bb1}$ $k_{TBB2,TET2} := k_{BB2,ET2}$

$k_{TAI1,blood} := s_t$ $k_{TBB2,blood} := s_t$

$k_{TAI2,Tbb1} := k_{AI2,bb1}$ $k_{TET2,S} := k_{ET2,S}$

$k_{TAI2,blood} := s_t$ $k_{TET2,blood} := s_t$

$k_{TAI3,Tbb1} := k_{AI3,bb1}$ $k_{TETseq,TLNet} := k_{ETseq,LNet}$

$k_{TAI3,TLNth} := k_{AI3,LNth}$ $k_{TETseq,blood} := s_t$

$k_{TAI3,blood} := s_t$ $k_{TBBseq,TLNth} := k_{BBseq,LNth}$

$k_{Tbb1,TBB1} := k_{bb1,BB1}$ $k_{TBBseq,blood} := s_t$

$k_{Tbb1,blood} := s_t$ $k_{Tbbseq,TLNth} := k_{bbseq,LNth}$

$k_{Tbb2,TBB1} := k_{bb2,BB1}$ $k_{Tbbseq,blood} := s_t$

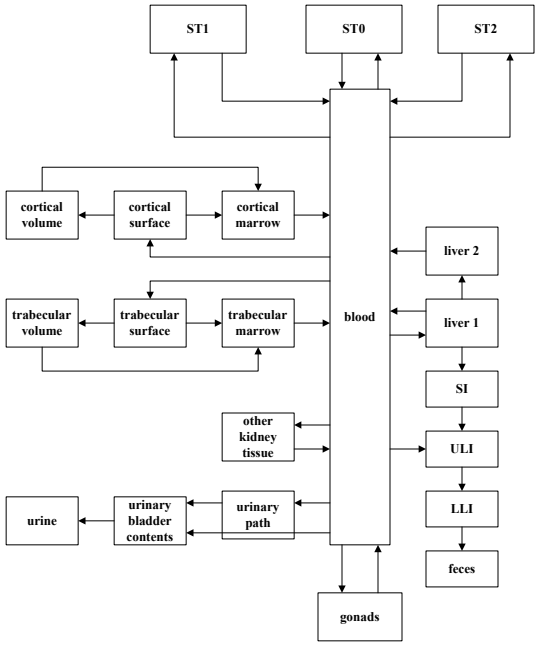
$k_{Tbb2,blood} := s_t$ $k_{TLNet,blood} := s_t$

$k_{TBB1,TET2} := k_{BB1,ET2}$ $k_{TLNth,blood} := s_t$

$k_{TBB1,blood} := s_t$

Define transfer rate constants for the ICRP 67 systemic model and GI tract model.

The ICRP 67 systemic model for plutonium and the ICRP GI tract models are shown below. The respiratory tract model feeds into the systemic model via the blood compartment and the GI tract model through the stomach (not shown).



$k_{blood,LIV1} := 0.1941$ $k_{blood,ST2} := 0.0129$ $k_{CS,CM} := 0.0000821$

$k_{blood,CS} := 0.1294$ $k_{ST0,blood} := 0.693$ $k_{TV,TM} := 0.000493$

$k_{blood,TS} := 0.1941$ $k_{UP,UBC} := 0.01386$ $k_{CV,CM} := 0.0000821$

$k_{blood,UBC} := 0.0129$ $k_{OKT,blood} := 0.00139$ $k_{CM,blood} := 0.0076$

$k_{blood,UP} := 0.00647$ $k_{ST1,blood} := 0.000475$ $k_{TM,blood} := 0.0076$

$k_{blood,OKT} := 0.00323$ $k_{ST1,UBC} := 0.000475$ $k_{LIV1,LIV2} := 0.00177$

$k_{blood,ULI} := 0.0129$ $k_{ST2,blood} := 0.000019$ $k_{LIV1,SI} := 0.000133$

$k_{blood,nads} := 0.00023$ $k_{TS,TV} := 0.000247$ $k_{LIV2,blood} := 0.000211$

$k_{blood,ST0} := 0.2773$ $k_{TS,TM} := 0.000493$ $k_{nads,blood} := 0.00019$

$k_{blood,ST1} := 0.0806$ $k_{CS,CV} := 0.0000411$ $k_{UBC,urine} := 12$ $k_{urine,urine} := 0$

Define transfer rate constants for the GI tract.

$f_1 := 5 \cdot 10^{-4}$ $\quad k_{S,SI} := 24$ $\quad k_{SI,ULI} := 6$

$k_{SI,blood} := \dfrac{k_{SI,ULI} \cdot f_1}{1 - f_1}$ $\quad k_{ULI,LLI} := \dfrac{24}{13}$ $\quad k_{LLI,feces} := 1$

Define total removal rate constants using the procedure *total*. For this case, the radioactive decay constant λ is set to zero (stable plutonium).

$\lambda \equiv 0$

$$\text{total}(k,\lambda) := \left| \begin{array}{l} K \leftarrow k \\ \text{for } comp \in 1..\text{cols}(k) \\ \quad \left| \begin{array}{l} K_{comp,comp} \leftarrow 0 \\ \text{for } j \in 1..\text{cols}(k) \\ \quad K_{comp,comp} \leftarrow K_{comp,comp} + k_{comp,j} \text{ if } comp \neq j \\ K_{comp,comp} \leftarrow -\left(K_{comp,comp} + \lambda\right) \end{array} \right. \\ K \end{array} \right.$$

$k := \text{total}(k,\lambda)$

Calculate eigenvalues and initial coefficients.

The eigenvalues γ and initial coefficients C_0 for the ICRP 66/67 plutonium model are calculated next with the procedure *coeff*. The content of any compartment in the model at any time after the intake can be calculated with the appropriate eigenvalues and coefficients.

$$\text{coeff}(k,q0) := \left| \begin{array}{l} q0 \leftarrow \text{submatrix}(q0,1,\text{rows}(k),1,1) \\ V \leftarrow \text{eigenvecs}\left(k^T\right) \\ M \leftarrow \text{lsolve}(V,q0) \\ \text{for } j \in 1..\text{cols}(k) \\ \quad \text{for } i \in 1..\text{cols}(k) \\ \quad\quad C_{i,j} \leftarrow V_{i,j} \cdot M_j \\ C \end{array} \right.$$

$\gamma := \text{eigenvals}\left(k^T\right)$

$C_0 := \text{coeff}(k,q0)$

Section 2. Define the urine bioassay data.

The following matrix of observed 24-hour urinary excretion of plutonium, e_{obs}, and associated time, t, were generated using the ICRP 66/67 biokinetic models defined above and the mechanistic chelation model define below. A little random noise was added to the excretion data to make it look more realistic.

$$\begin{pmatrix} t \\ y \end{pmatrix} :=$$

1	0.9861
2	9.1829
3	4.9901
4	2.8553
5	1.7506
6	1.2311
7	0.9187
8	0.7570
9	0.6793
10	0.5839
11	0.5357
12	0.4939
13	0.4615
14	0.4291
15	0.3794

t has units of days and e_{obs} units of Bq

NumUrine := rows(t) $e_{obs} := y \cdot Bq$

Times τ that the person was chelated are listed below. For simplicity, the time of chelation is *almost* always presented as the beginning of the day on which the chelation actually occurred. For example, if an individual was chelated 1.2 days after the intake, then τ is assumed to be 1 day after intake. The only exceptions to this general rule are:

1) If the time of chelation is quite close to the next day, like 1.9 days after intake, τ may be taken to be 2 days after intake.

2) In the mechanistic model, the first chelation cannot be at t=0 because there is no plutonium in the blood at that time. This is not a problem with the Hall model, which can have τ = 0.

$$\tau := \begin{pmatrix} 1 \\ 50 \\ 100 \end{pmatrix}$$

NumChel := rows(τ) NumChel = 3

Section 3. Evaluate data with the mechanistic method.

The incremental urinary excretion function for the excretion of unchelated plutonium is

$$i_u(t,\tau,C) := \sum_{i=AI1}^{urine} C_{urine,i}\cdot\exp\left[\gamma_i\cdot(t-\tau)\right] - \sum_{i=AI1}^{urine} C_{urine,i}\cdot\exp\left[\gamma_i\cdot\left[t-(\tau+1)\right]\right]$$

The function *Newq0* calculates compartment contents after a chelation. This function assumes that each chelation will remove a fraction E_{blood} of the total plutonium that is in the bloodstream and Eliv from the liver-1 compartment. Thes parameters are adjusted as need to achieve an adequate fit to the observed urinary excretion.

$$\text{Newq0}(q0,\tau,C) := \left|\begin{array}{l} \text{for } comp \in AI1 .. urine \\ \quad Newq0_{comp} \leftarrow \sum_{i=AI1}^{urine} C_{comp,i}\cdot\exp(\gamma_i\cdot\tau) \\ Newq0_{urine+1} \leftarrow F_{blood}\cdot Newq0_{blood} + F_{liv}\cdot Newq0_{LIV1} \\ Newq0_{LIV1} \leftarrow (1-F_{liv})\cdot Newq0_{LIV1} \\ Newq0_{blood} \leftarrow (1-F_{blood})\cdot Newq0_{blood} \\ Newq0 \end{array}\right.$$

$F_{liv} \equiv 0.023$

$F_{blood} \equiv 0.5$

The incremental urinary excretion function for the excretion of Pu-DTPA chelate, i_c, is shown below. This is the same function used in the Hall model.

$$f_c(t,\tau) := 0.95\cdot\exp\left[\frac{-\ln(2)\cdot(t-\tau)}{1}\right] + 0.05\cdot\exp\left[\frac{-\ln(2)\cdot(t-\tau)}{10}\right]$$

$$k_n := \left|\begin{array}{l} i \leftarrow 0 \\ sum \leftarrow 0 \\ ratio \leftarrow 1 \\ \text{while } ratio > 10^{-6} \\ \quad \left|\begin{array}{l} i \leftarrow i+1 \\ sum \leftarrow sum + f_c(i,0) \\ ratio \leftarrow \frac{f_c(i,0)}{sum} \end{array}\right. \\ \frac{1}{sum} \end{array}\right.$$

$k_n = 0.60731$

$$i_c(t,\tau) := \left|\begin{array}{ll} 0 & \text{if } t \le \tau \\ k_n\cdot f_c(t,\tau) & \text{otherwise} \end{array}\right.$$

The urinary excretion prior to the first intake (day 1) is calculated with C_0.

$i := 1$

$C := coeff(k, q0)$ this is the same as C_0

$\varepsilon_i := i_u(t_i, 0, C)$

Next, the model is stopped at the time of the first chelation, the content of each compartment at that time is calculated, the chelate is removed from the blood compartment, and the model restarted with the new initial contents. This new model is valid until the time of the next chelation. Note that K is defined the same as in Hall's model.

$i := 2 .. 50$

$q0 := Newq0(q0, \tau_1, C)$

$K_1 := q0_{urine+1}$ $K_1 = 0.00561$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_1, C) + K_1 \cdot i_c(t_i, \tau_1)$

Do the same for the second chelation.

$i := 51 .. 100$

$q0 := Newq0(q0, \tau_2, C)$

$K_2 := q0_{urine+1}$ $K_2 = 0.00049$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_2, C) + K_1 \cdot i_c(t_i, \tau_1) + K_2 \cdot i_c(t_i, \tau_2)$

And the third.

$i := 101 .. 300$

$q0 := Newq0(q0, \tau_3, C)$

$K_3 := q0_{urine+1}$ $K_3 = 0.00045$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_3, C) + K_1 \cdot i_c(t_i, \tau_1) + K_2 \cdot i_c(t_i, \tau_2) + K_3 \cdot i_c(t_i, \tau_3)$

Calculate the intake using an unweighted least-squares fit.

$$I := \left[\left(\varepsilon^{T}\cdot\varepsilon\right)^{-1}\cdot\left(\varepsilon^{T}\cdot e_{obs}\right)\right]_1 \qquad I = 4973.97227\ \text{Bq}$$

The real answer is 5000 Bq.

The quantity q of plutonium removed by the three chelations is

$$q := \sum_{i=1}^{NumChel} I\cdot K_i \qquad q = 32.56933\ \text{Bq}$$

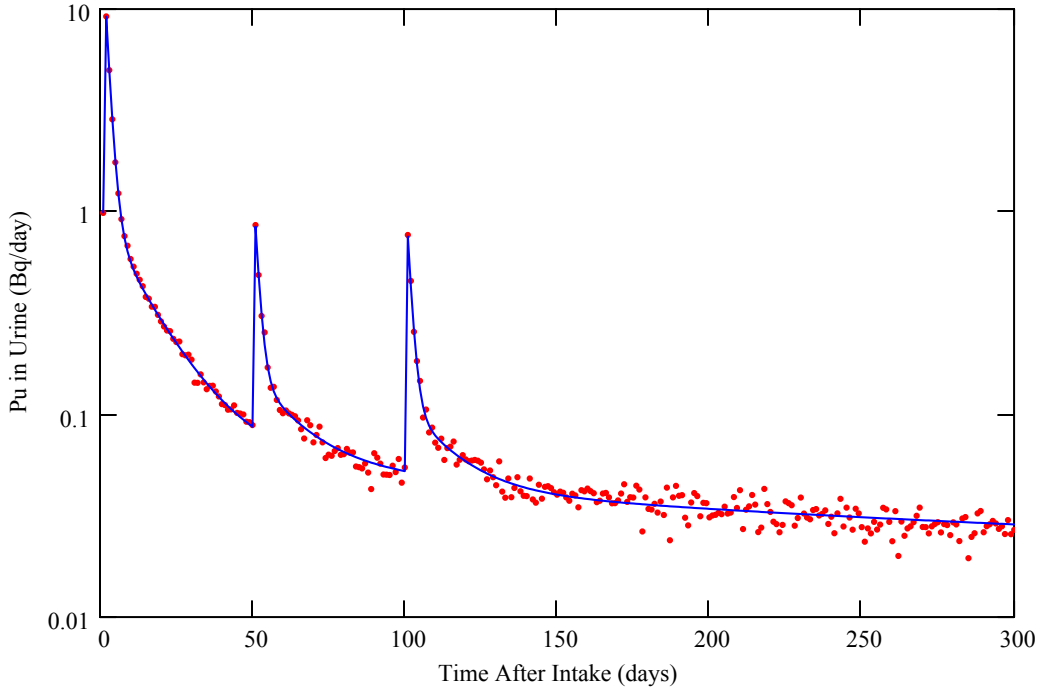
The effective intake is

$$I_{eff} := I - q \qquad I_{eff} = 4941.40294\ \text{Bq}$$

And the predicted urinary excretion is:

$$e_{exp} := \varepsilon\cdot I$$

$$i := 1\ ..\ NumUrine$$



The intake to dose conversion factors for Type M plutonium and injected plutonium are

$$DCF_m := 3.31\cdot10^{-5}\cdot\frac{Sv}{Bq} \qquad DCF_{inj} := 5.03\cdot10^{-4}\cdot\frac{Sv}{Bq}$$

The dose calculated from the intake is

$$I \cdot DCF_m = 0.16464\,Sv$$

The dose calculated from the effective intake is

$$I_{eff} \cdot DCF_m = 0.16356\,Sv$$

The dose calculated assuming q gives the same dose as an injection of plutonium is

$$I \cdot DCF_m - q \cdot DCF_{inj} = 0.14826\,Sv$$

Section 4. Evaluate data with Hall's method.

The chelation enhancement factor E as defined in Equation 6 is

$$E \equiv 18.5$$

The enhancement factor was selected to best fit the urinary excretion data. The fraction K of an intake removed by chelation as defined in Equation 8 is

$$K(E,t,\tau) := \begin{cases} 0 & \text{if } t \le \tau \\ \dfrac{\left[i_u(\tau + 1,0,C_0)\cdot(E-1)\right]}{i_c(1,0) - i_u(\tau + 1,0,C_0)} & \text{otherwise} \end{cases}$$

The matrix of apparent excretion fractions is calculated next.

$$\varepsilon_i := i_u(t_i,0,C_0)\cdot \prod_{j=1}^{NumChel} \left(1 - K(E,t_i,\tau_j)\right) + \sum_{j=1}^{NumChel} K(E,t_i,\tau_j)\cdot i_c(t_i,\tau_j)$$

The intake of total alpha Pu is calculated using an unweighted least-squares fit as given in Equation 16.

$$I := \left[\left(\varepsilon^T\cdot\varepsilon\right)^{-1}\cdot\left(\varepsilon^T\cdot e_{obs}\right)\right]_1 \qquad I = 4312.39963\,Bq$$

The fraction of the intake removed by chelation is

$$K_1 := \frac{\left[i_u(\tau_1 + 1,0,C_0)\cdot(E-1)\right]}{i_c(1,0) - i_u(\tau_1 + 1,0,C_0)} \qquad K_1 = 0.00635$$

$$K_2 := \frac{\left[i_u(\tau_2 + 1,0,C_0)\cdot(E-1)\right]}{i_c(1,0) - i_u(\tau_2 + 1,0,C_0)} \qquad K_2 = 0.00069$$

$$K_3 := \frac{\left[i_u(\tau_3 + 1, 0, C_0)\cdot(E - 1)\right]}{i_c(1,0) - i_u(\tau_3 + 1, 0, C_0)} \qquad K_3 = 0.00058$$

The quantity q of plutonium removed by the three chelations is

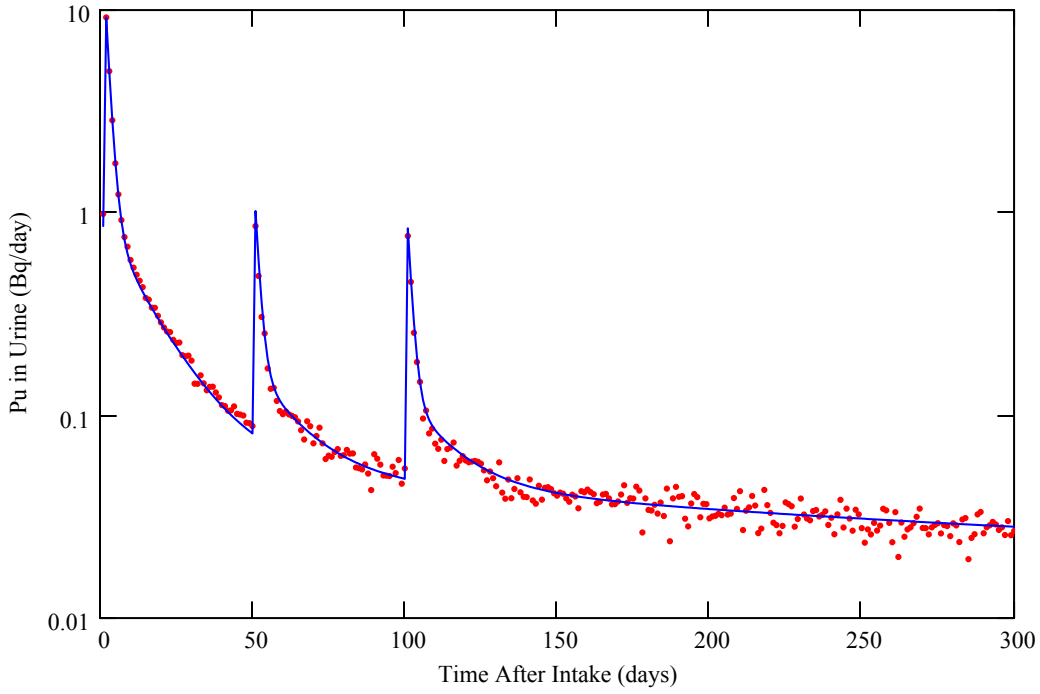
$$q := \sum_{i=1}^{NumChel} I\cdot K_i \qquad q = 32.86002\,Bq$$

The effective intake is

$$I_{eff} := I - q \qquad I_{eff} = 4279.53961\,Bq$$

The expectation urinary excretion is calculated next.

$$e_{exp} := \varepsilon\cdot I$$



The dose calculated from the intake is

$$I\cdot DCF_m = 0.14274\,Sv$$

The dose calculated from the effective intake is

$$I_{eff}\cdot DCF_m = 0.14165\,Sv$$

The dose calculated assuming q gives the same dose as an injection of plutonium is

$I \cdot DCF_m - q \cdot DCF_{inj} = 0.12621\ Sv$

Section 5. Evaluate data with Jech's method.

In Jech's method we just ignore the urinary excretion influenced by chelation therapy and evaluate the remanding data with the usual models and methods. This leads us directly to the I_{eff} with no estimate of or q.

$\varepsilon := 0$

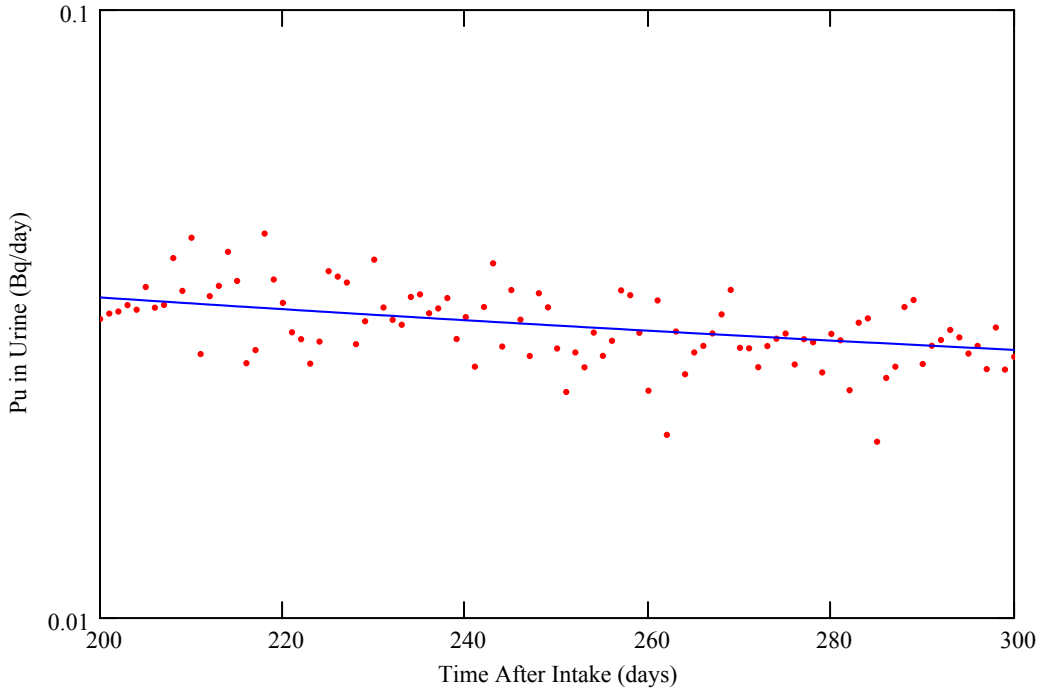
$i := 200 .. 300$

$e_{u_i} := i_u(t_i, 0, C_0)$

$I_{eff} := \left[\left(e_u^T \cdot e_u \right)^{-1} \cdot \left(e_u^T \cdot e_{obs} \right) \right]_1 \qquad I_{eff} = 4188.70053\ Bq$

Note the similarity of the effective intakes calculated from the Hall and Jech methods.

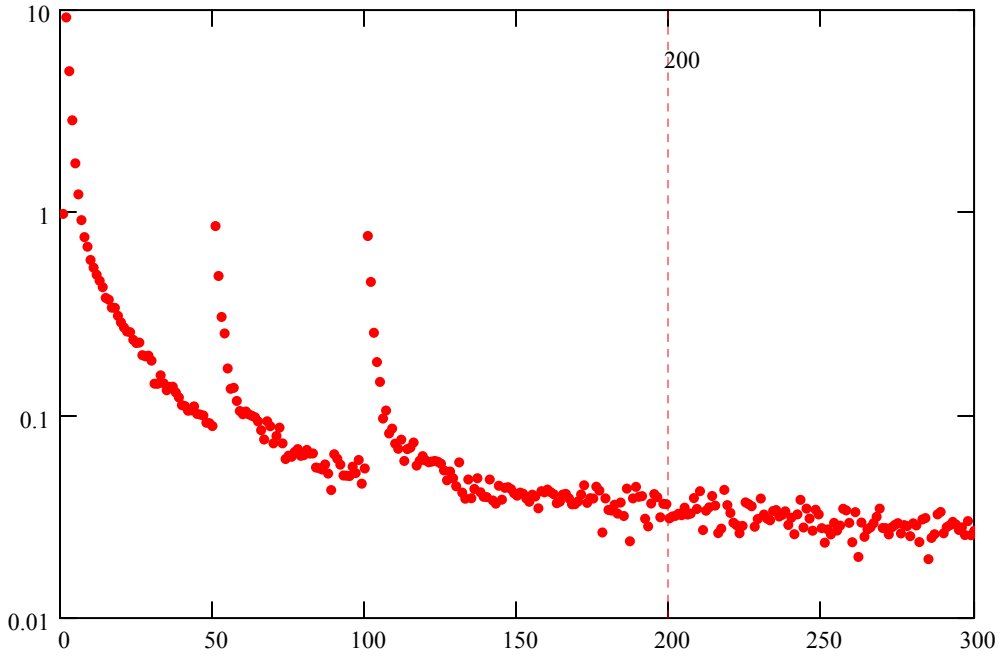
$e_{exp_i} := e_{u_i} \cdot I_{eff}$



$I_{eff} \cdot DCF_m = 0.13865\ Sv$

Plot of urine bioassay data. The effects of chelation are assumed to completely subside after 100 days.

$i := 1 .. 300$



Appendix B. A Review of Hall's Method for Evaluating Urinary Excretion following Chelation Therapy.

The nomenclature used in the previous discussion of Hall's model has been changed slightly here to more closely match the nomenclature used in Mathcad worksheets. The quantity of plutonium $e_{exp}(t)$ predicted to be in a 24-hour urine sample collected from t-1 days to t days after an instantaneous intake I is given by Equation B1.

$$e_{\exp}(t) = I\, i_u(t) \qquad (B1)$$

Unless otherwise noted, all times have the unit of days. In Equation B1, $i_u(t)$ is the excretion function that gives the fraction of an intake expected to be in a 24-hour incremental urine sample collected from t-1 days to t days after the intake. By convention, this urine sample is said to have been collected at time t, the time at which the 24-hour urine sample was completed. Note that the smallest value t can have is 1, i.e., a 24-hour urine sample cannot be collected at any time before t = 1 day. The restriction that t must be greater than or equal to 1 is understood to apply to all excretion functions in this discussion and will no longer be explicitly stated. To simplify the derivation of Hall's method, we will further restrict the evaluation of excretion functions to integer times such as t = 1 day. Functions will not be evaluated at times such as t = 1.5 days.

If we assume that an individual is chelated at time τ after an acute intake, Equation B1 is applicable for times $t \le \tau$. For example, if the person is chelated at time τ=2 days after an intake, Equation B1 describes the urinary excretion at times t=1 day and t=2 days. The chelation is always assumed to take place at integer times such as τ=0 days. Chelation is assumed not to occur at a fractional time such as τ=1.5 days.

At times $t > \tau$, the following equation describes the urinary excretion of the plutonium:

$$e_{\exp}(t) = (I - q)\, i_u(t) + q\, i_c(t - \tau) \qquad (B2)$$

where

q = quantity of plutonium ultimately removed by the chelation at time τ,
τ = time after an acute intake that the chelation agent was administered, and
$i_c(t - \tau)$ = fraction of q that is excreted in the urine at time t .

Note that whenever the term $(t-\tau)$ appears, it is understood that t must be greater than τ. Equation B2 embodies the three fundamental assumptions used in the Hall method of evaluating intakes following chelation therapy:

- At the time τ the chelation agent is administered, there is a quantity q of plutonium that is available, or will be available in the following 24 hours, to form a chelate. The plutonium can come from any intake that occurred prior to the chelation.
- The chelate is stable, i.e., it will not separate back into plutonium and the chelation agent, and will be excreted with its own excretion function i_c rather than that of plutonium i_u.
- The biokinetics of the plutonium that was not chelated will be unaffected by the chelation except the intake will appear to be reduced from I to I - q.

The incremental urinary excretion function i_c for the chelate usually takes the following form:

$$i_c(t - \tau) = k_n\left(C_1 e^{-k_1(t-\tau)} + C_2 e^{-k_2(t-\tau)}\right) \qquad (B3)$$

where the coefficients C and rate constants k are determined empirically for each case. This function gives the fraction of q that is expected to be in a 24-hour urine sample collected at time t after intake and t - τ after chelation. Note that the exponentials in Equation 4 do not necessarily sum to 1 over an infinite length of time, which is an undesirable characteristic for an incremental excretion function. To make i_c sum to one, we must multiply by a normalization constant k_n, which is calculated as follows[g]:

$$k_n = \frac{1}{\sum_{t=1}^{\infty} i_c(t-\tau)} \qquad (B4)$$

In practice, the terms of i_c are summed until k_n does not change by more than 10^{-6}. The following function is used in this report:

$$i_c(t-\tau) = 0.6073\left[0.95e^{\frac{-\ln(2)(t-\tau)}{1}} + 0.05e^{\frac{-\ln(2)(t-\tau)}{10}}\right] \qquad (B5)$$

As Equation B5 implies, the perturbation of the urinary excretion pattern caused by chelation therapy will usually subside within about 100 days following the chelation. Thus, the easiest way to evaluate an intake following chelation therapy is to model the urinary excretion data collected after the 100-day cutoff using standard biokinetic models (Jech's method). This method is the easiest because, according to the fundamental assumptions given above, this evaluation will give the "effective" intake I - q and we never have to find q.

Rather than waiting to evaluate the long-term urinary excretion data, we frequently want to solve Equation B2 to estimate the intake before the effects of chelation have subsided. One reason for this impatience is that management and regulatory agencies often request intake estimates within a month or so of the intake. Another reason to solve Equation B2 is to calculate q so that the effectiveness of the chelation may be estimated.

The problem with trying to solve Equation B2 is that it contains two unknowns, I and q. One way to eliminate the unknown q from Equation B2 is through the use of the excretion enhancement ratio E. E is the ratio of the urinary excretion of plutonium on the day of the chelation to the urinary excretion that would be expected on the same day if there were no chelation:

$$E = \frac{(I-q)i_u(\tau+1) + q\,i_c(1)}{I\,i_u(\tau+1)} \qquad (B6)$$

Equation B6 can be rearranged to give the following relationship:

$$I\left[\frac{i_u(\tau+1)(E-1)}{i_c(1)-i_u(\tau+1)}\right] = q \qquad (B7)$$

[g] The normalization constant was inadvertently omitted from the paper presented at the 1994 Summer School. Thanks to Dr. Clayton French for pointing out the error.

The factor in the square brackets, which we will call K, is the fraction of the intake that is expected to be removed by the chelation.

$$K = \left[\frac{i_u(\tau+1)(E-1)}{i_c(1) - i_u(\tau+1)} \right] \qquad (B8)$$

Substituting K into Equation B2 and simplifying gives the following, which has only one unknown, I:

$$e_{\exp}(t) = I\left[(1-K)\, i_u(t) + K\, i_c(t-\tau)\right] \qquad (B9)$$

Equation B9 describes the urinary excretion of plutonium at times $t > \tau$. If there is a second chelation, the time of the first chelation is referred to as τ_1 and the time of the second chelation as τ_2. The following equation describes the urinary excretion of the plutonium at times $t > \tau_2 > \tau_1$ after intake:

$$e_{\exp}(t) = I\left[(1-K_1)(1-K_2)\, i_u(t) + K_1\, i_c(t-\tau_1) + K_2\, i_c(t-\tau_2)\right] \qquad (B10)$$

Again, K_1 refers to the first chelation and K_2 to the second. This assumes that the effects of each chelation are independent of the effects of all other chelations. In the general case, if there are N chelations, the urinary excretion of plutonium at times $t > \tau_N$ after the last chelation is given by the following equation:

$$e_{\exp}(t) = I\left[i_u(t) \prod_{j=1}^{N} (1-K_j) + \sum_{j=1}^{N} K_j\, i_c(t-\tau_j) \right] \qquad (B11)$$

Appendix C. Generation of Urine Bioassay Data for Benchmarking

The Hall method was developed from real intake cases and was designed to predict patterns in urinary excretion of plutonium following chelation therapy. Therefore, if we use reasonable default parameters and models in the Hall method we can generate realistic urinary excretion data in any desired form. More specifically, to generate a given set of urinary excretion data with the Hall method, we must specify the following models and parameters:

1. The biokinetic models used to calculate the urinary excretion fractions.
2. The chelate excretion function i_c.
3. The enhancement factor E.
4. The times of chelation.
5. The number of urine samples and their void times.

Note that the specification of the biokinetic model includes parameters such as the solubility of the material, mode of intake, etc.

Once the "synthetic" data are generated, we can evaluate it with the mechanistic model using all of the default parameters common with Hall's method (everything except for item 3 above). By trial and error, we can then modify the chelation removal fractions F for each compartment in the mechanistic method until reasonable agreement with the data is achieved. When we are done we have a realistic set of urinary excretion data, completely specified in every detail, that are adequately modeled by two different methods. Random noise was added to the urinary excretion data to lend them a bit of realism. The attached Mathcad worksheet documents how the benchmark data were generated for an inhalation intake of Type M plutonium aerosols.

Benchmark Chelation Data

Generate synthetic urinary excretion data for plutonium following chelation therapy. Acute inhalation intake of Type M aerosol. Implemented in Mathcad 2001i.

Section 1. Define the ICRP 66/67 urinary excretion function

In the first section of this worksheet, we will derive the eigenvalues and coefficients that define the retention functions for all compartments of the ICRP 66/67 biokinetic model.

ORIGIN ≡ 1 Defines arrays to begin with the 1,1 element.

The compartments in the model are assigned numbers to clarify their use in the arrays to be defined.

Respiratory tract compartments. Inhaled particles are deposited in compartments AI1 through ET1.

AI1 := 1	bb1 := 4	BB1 := 7	ET2 := 10	LNet := 13
AI2 := 2	bb2 := 5	BB2 := 8	ETseq := 11	LNth := 14
AI3 := 3	bbseq := 6	BBseq := 9	ET1 := 12	

Transformed respiratory tract compartments.

TAI1 := 15	Tbb1 := 18	TBB1 := 21	TET2 := 24	TLNth := 27
TAI2 := 16	Tbb2 := 19	TBB2 := 22	TETseq := 25	
TAI3 := 17	Tbbseq := 20	TBBseq := 23	TLNet := 26	

GI tract compartments and feces.

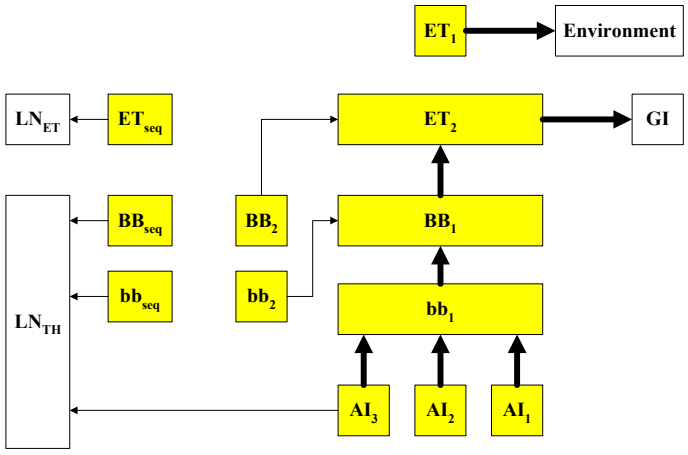
S := 28 SI := 29 ULI := 30 LLI := 31

Systemic compartments of the ICRP 67 plutonium model.

blood := 32	ST0 := 35	CV := 38	TV := 41	OKT := 44	nads := 47	feces := 49
LIV1 := 33	ST1 := 36	CS := 39	TS := 42	UP := 45	ENV := 48	urine := 50
LIV2 := 34	ST2 := 37	CM := 40	TM := 43	UBC := 46		

Define initial deposition in compartments of the respiratory tract.

The mechanical clearance model for the respiratory tract is shown below. Inhaled particles are deposited in the twelve compartments highlighted in yellow. The fractions of particles deposited in compartments AI1 through ET1 following an inhalation intake of 1.0 mm AMAD aerosol are assigned to q0. These values are taken from tables in the ICRP CD.

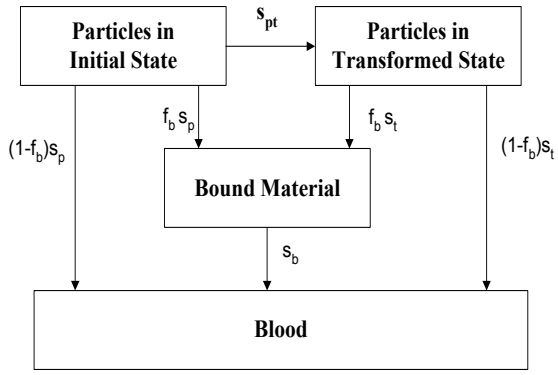


$$q0 := \begin{pmatrix} 0.03198 \\ 0.06396 \\ 0.01066 \\ 0.00833 \\ 0.00809 \\ 0.00012 \\ 0.00649 \\ 0.00584 \\ 8.694 \times 10^{-5} \\ 0.2111 \\ 0.00011 \\ 0.1652 \end{pmatrix}$$

$$q0_{urine} := 0$$

Define particle dissolution model. All rate constants are in units of 1/days.

The dissolution model for the respiratory tract is shown below. Defaults for Type M material are f_r=0.1, s_r=100, s_s=0.005, and f_b=0.



$f_r \equiv 0.1$ $s_r \equiv 100$ $s_s \equiv 0.005$

$s_p := s_s + f_r \cdot (s_r - s_s)$ $s_{pt} := (1 - f_r) \cdot (s_r - s_s)$ $s_t := s_s$

$s_p = 10.00450$ $s_{pt} = 89.99550$ $s_t = 0.00500$

Define transfer rate constants for the respiratory tract compartments.

$k_{AI1,bb1} := 0.02$ $k_{bb2,BB1} := 0.03$ $k_{ETseq,LNet} := 0.001$

$k_{AI1,blood} := s_p$ $k_{bb2,blood} := s_p$ $k_{ETseq,blood} := s_p$

$k_{AI1,TAI1} := s_{pt}$ $k_{bb2,Tbb2} := s_{pt}$ $k_{ETseq,TETseq} := s_{pt}$

$k_{AI2,bb1} := 0.001$ $k_{BB1,ET2} := 10$ $k_{BBseq,LNth} := 0.01$

$k_{AI2,blood} := s_p$ $k_{BB1,blood} := s_p$ $k_{BBseq,blood} := s_p$

$k_{AI2,TAI2} := s_{pt}$ $k_{BB1,TBB1} := s_{pt}$ $k_{BBseq,TBBseq} := s_{pt}$

$k_{AI3,bb1} := 0.0001$ $k_{BB2,ET2} := 0.03$ $k_{bbseq,LNth} := 0.01$

$k_{AI3,LNth} := 0.00002$ $k_{BB2,blood} := s_p$ $k_{bbseq,blood} := s_p$

$k_{AI3,blood} := s_p$ $k_{BB2,TBB2} := s_{pt}$ $k_{bbseq,Tbbseq} := s_{pt}$

$k_{AI3,TAI3} := s_{pt}$ $k_{ET2,S} := 100$ $k_{LNth,TLNth} := s_{pt}$

$k_{bb1,BB1} := 2$ $k_{ET2,blood} := s_p$ $k_{LNet,blood} := s_p$

$k_{bb1,blood} := s_p$ $k_{ET2,TET2} := s_{pt}$ $k_{LNet,TLNet} := s_{pt}$

$k_{bb1,Tbb1} := s_{pt}$ $k_{ET1,ENV} := 1$ $k_{LNth,blood} := s_p$

Define transfer rate constants for the transformed respiratory tract compartments.

$k_{TAI1,Tbb1} := k_{AI1,bb1}$ $k_{TBB2,TET2} := k_{BB2,ET2}$

$k_{TAI1,blood} := s_t$ $k_{TBB2,blood} := s_t$

$k_{TAI2,Tbb1} := k_{AI2,bb1}$ $k_{TET2,S} := k_{ET2,S}$

$k_{TAI2,blood} := s_t$ $k_{TET2,blood} := s_t$

$k_{TAI3,Tbb1} := k_{AI3,bb1}$ $k_{TETseq,TLNet} := k_{ETseq,LNet}$

$k_{TAI3,TLNth} := k_{AI3,LNth}$ $k_{TETseq,blood} := s_t$

$k_{TAI3,blood} := s_t$ $k_{TBBseq,TLNth} := k_{BBseq,LNth}$

$k_{Tbb1,TBB1} := k_{bb1,BB1}$ $k_{TBBseq,blood} := s_t$

$k_{Tbb1,blood} := s_t$ $k_{Tbbseq,TLNth} := k_{bbseq,LNth}$

$k_{Tbb2,TBB1} := k_{bb2,BB1}$ $k_{Tbbseq,blood} := s_t$

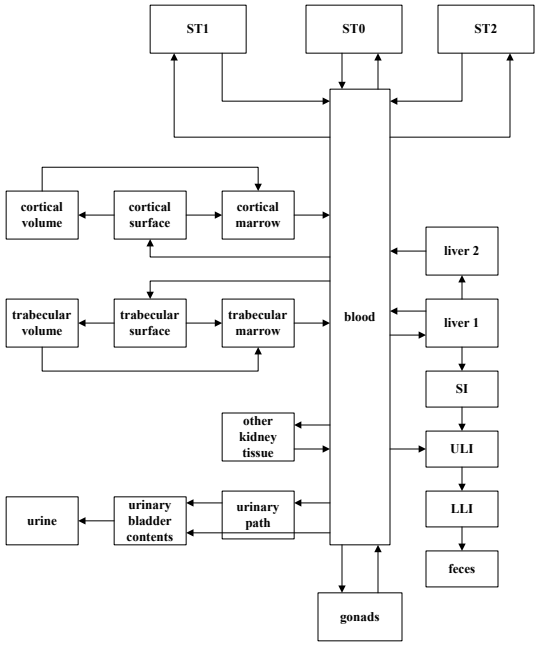
$k_{Tbb2,blood} := s_t$ $k_{TLNet,blood} := s_t$

$k_{TBB1,TET2} := k_{BB1,ET2}$ $k_{TLNth,blood} := s_t$

$k_{TBB1,blood} := s_t$

Define transfer rate constants for the ICRP 67 systemic model and GI tract model.

The ICRP 67 systemic model for plutonium and the ICRP GI tract models are shown below. The respiratory tract model feeds into the systemic model via the blood compartment and the GI tract model through the stomach (not shown).



$k_{blood,LIV1} := 0.1941$ $k_{blood,ST2} := 0.0129$ $k_{CS,CM} := 0.0000821$

$k_{blood,CS} := 0.1294$ $k_{ST0,blood} := 0.693$ $k_{TV,TM} := 0.000493$

$k_{blood,TS} := 0.1941$ $k_{UP,UBC} := 0.01386$ $k_{CV,CM} := 0.0000821$

$k_{blood,UBC} := 0.0129$ $k_{OKT,blood} := 0.00139$ $k_{CM,blood} := 0.0076$

$k_{blood,UP} := 0.00647$ $k_{ST1,blood} := 0.000475$ $k_{TM,blood} := 0.0076$

$k_{blood,OKT} := 0.00323$ $k_{ST1,UBC} := 0.000475$ $k_{LIV1,LIV2} := 0.00177$

$k_{blood,ULI} := 0.0129$ $k_{ST2,blood} := 0.000019$ $k_{LIV1,SI} := 0.000133$

$k_{blood,nads} := 0.00023$ $k_{TS,TV} := 0.000247$ $k_{LIV2,blood} := 0.000211$

$k_{blood,ST0} := 0.2773$ $k_{TS,TM} := 0.000493$ $k_{nads,blood} := 0.00019$

$k_{blood,ST1} := 0.0806$ $k_{CS,CV} := 0.0000411$ $k_{UBC,urine} := 12$ $k_{urine,urine} := 0$

Define transfer rate constants for the GI tract.

$f_1 := 5 \cdot 10^{-4}$ $\quad k_{S,SI} := 24$ $\quad k_{SI,ULI} := 6$

$k_{SI,blood} := \dfrac{k_{SI,ULI} \cdot f_1}{1 - f_1}$ $\quad k_{ULI,LLI} := \dfrac{24}{13}$ $\quad k_{LLI,feces} := 1$

Define total removal rate constants using the procedure *total*. For this case, the radioactive decay constant λ is set to zero (stable plutonium).

$\lambda \equiv 0$

$$\text{total}(k,\lambda) := \left| \begin{array}{l} K \leftarrow k \\ \text{for } comp \in 1..\text{cols}(k) \\ \quad \left| \begin{array}{l} K_{comp,comp} \leftarrow 0 \\ \text{for } j \in 1..\text{cols}(k) \\ \quad K_{comp,comp} \leftarrow K_{comp,comp} + k_{comp,j} \text{ if } comp \neq j \\ K_{comp,comp} \leftarrow -\left(K_{comp,comp} + \lambda\right) \end{array} \right. \\ K \end{array} \right.$$

$k := \text{total}(k,\lambda)$

Calculate eigenvalues and initial coefficients.

The eigenvalues γ and initial coefficients C_0 for the ICRP 66/67 plutonium model are calculated next with the procedure *coeff*. The content of any compartment in the model at any time after the intake can be calculated with the appropriate eigenvalues and coefficients.

$$\text{coeff}(k,q0) := \left| \begin{array}{l} q0 \leftarrow \text{submatrix}(q0,1,\text{rows}(k),1,1) \\ V \leftarrow \text{eigenvecs}\left(k^T\right) \\ M \leftarrow \text{lsolve}(V,q0) \\ \text{for } j \in 1..\text{cols}(k) \\ \quad \text{for } i \in 1..\text{cols}(k) \\ \quad\quad C_{i,j} \leftarrow V_{i,j} \cdot M_j \\ C \end{array} \right.$$

$\gamma := \text{eigenvals}\left(k^T\right)$

$C_0 := \text{coeff}(k,q0)$

Section 2. Generate data with the mechanistic method.

We will generate 300 urine results for days 1 through 300 after intake.

$$NumUrine := 300$$

$$i := 1 .. NumUrine$$

$$t_i := i$$

Times τ that the person was chelated are listed below. For simplicity, the time of chelation is *almost* always presented as the beginning of the day on which the chelation actually occurred. For example, if an individual was chelated 1.2 days after the intake, then τ is assumed to be 1 day after intake. The only exceptions to this general rule are:

1) If the time of chelation is quite close to the next day, like 1.9 days after intake, τ may be taken to be 2 days after intake.

2) In the mechanistic model, the first chelation cannot be at t=0 because there is no plutonium in the blood at that time. This is not a problem with the Hall model, which can have $\tau = 0$.

$$\tau := \begin{pmatrix} 1 \\ 50 \\ 100 \end{pmatrix}$$

$$NumChel := rows(\tau) \qquad NumChel = 3$$

The incremental urinary excretion function for the excretion of unchelated plutonium is

$$i_u(t,\tau,C) := \sum_{i=AI1}^{urine} C_{urine,i}\cdot\exp\left[\gamma_i\cdot(t-\tau)\right] - \sum_{i=AI1}^{urine} C_{urine,i}\cdot\exp\left[\gamma_i\cdot\left[t-(\tau+1)\right]\right]$$

The function *Newq0* calculates compartment contents after a chelation. This function assumes that each chelation will remove a fraction E_{blood} of the total plutonium that is in the bloodstream and E_{liv} that is in the liver-1 compartment.

$$Newq0(q0,\tau,C) := \left| \begin{array}{l} \text{for } comp \in AI1 .. urine \\ \quad Newq0_{comp} \leftarrow \sum_{i=AI1}^{urine} C_{comp,i}\cdot\exp(\gamma_i\cdot\tau) \\ Newq0_{urine+1} \leftarrow E_{blood}\cdot Newq0_{blood} + E_{liv}\cdot Newq0_{LIV1} \\ Newq0_{LIV1} \leftarrow (1-E_{liv})\cdot Newq0_{LIV1} \\ Newq0_{blood} \leftarrow (1-E_{blood})\cdot Newq0_{blood} \\ Newq0 \end{array} \right.$$

$$E_{blood} \equiv 0.5$$

$$E_{liv} \equiv 0.023$$

The incremental urinary excretion function for the excretion of Pu-DTPA chelate, i_c, is shown below. This is the same function used in the Hall model.

$$f_c(t,\tau) := 0.95\cdot\exp\left[\frac{-\ln(2)\cdot(t-\tau)}{1}\right] + 0.05\cdot\exp\left[\frac{-\ln(2)\cdot(t-\tau)}{10}\right]$$

$k_n :=$
- $i \leftarrow 0$
- $sum \leftarrow 0$
- $ratio \leftarrow 1$
- while $ratio > 10^{-6}$
  - $i \leftarrow i + 1$
  - $sum \leftarrow sum + f_c(i,0)$
  - $ratio \leftarrow \frac{f_c(i,0)}{sum}$
- $\frac{1}{sum}$

$$i_c(t,\tau) := \begin{cases} 0 & \text{if } t \le \tau \\ k_n\cdot f_c(t,\tau) & \text{otherwise} \end{cases}$$

The urinary excretion prior to the first intake (day 1) is calculated with C_0.

$i := 1$

$C := coeff(k, q0)$ this is the same as C_0

$\varepsilon_i := i_u(t_i, 0, C)$

Next, the model is stopped at the time of the first chelation, the content of each compartment at that time is calculated, the chelate is removed from the blood compartment, and the model restarted with the new initial contents. This new model is valid until the time of the next chelation. Note that K is defined the same as in Hall's model.

$i := 2..50$

$q0 := Newq0(q0, \tau_1, C)$

$K_1 := q0_{urine+1}$ $K_1 = 0.00561$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_1, C) + K_1\cdot i_c(t_i, \tau_1)$

Do the same for the second chelation.

$i := 51 .. 100$

$q0 := Newq0(q0, \tau_2, C)$

$K_2 := q0_{urine+1}$ $\quad K_2 = 0.00049$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_2, C) + K_1 \cdot i_c(t_i, \tau_1) + K_2 \cdot i_c(t_i, \tau_2)$

And the third.

$i := 101 .. 300$

$q0 := Newq0(q0, \tau_3, C)$

$K_3 := q0_{urine+1}$ $\quad K_3 = 0.00045$

$C := coeff(k, q0)$

$\varepsilon_i := i_u(t_i, \tau_3, C) + K_1 \cdot i_c(t_i, \tau_1) + K_2 \cdot i_c(t_i, \tau_2) + K_3 \cdot i_c(t_i, \tau_3)$

The intake is defined to be

$I := 5000 \cdot Bq$

The quantity q of plutonium removed by the three chelations is

$q := \sum_{i=1}^{NumChel} I \cdot K_i$ $\quad q = 32.73975\ Bq$

The effective intake is

$I_{eff} := I - q$ $\quad I_{eff} = 4967.26025\ Bq$

The predicted urinary excretion is calculated below, with a little random noise added to the excretion data to make it look more realistic.

$i := 1 .. NumUrine$

$e_{obs_i} := rnorm(1, 5000 \cdot \varepsilon_i, \sqrt{0.0005 \cdot 5000 \cdot \varepsilon_i})_1 \cdot Bq$

Note that the predicted urinary excretion data calculated here will be different every time the worksheet is recalculated because of the random error added to the mean urinary excretion.

1	0.986101
2	9.182905
3	4.990082
4	2.855259
5	1.750576
6	1.231064
7	0.918671
8	0.756986
9	0.679338
10	0.583851

$(t \quad e_{obs})$

Calculate the intake using an unweighted least-squares fit.

$$I := \left[\left(\varepsilon^{T}\cdot\varepsilon\right)^{-1}\cdot\left(\varepsilon^{T}\cdot e_{obs}\right)\right]_1 \qquad I = 4973.97227\,\text{Bq}$$

And the predicted urinary excretion is:

$e_{exp} := \varepsilon \cdot I$

$i := 1 .. NumUrine$